# Interrelations between cognitive dysfunction and motor symptoms of Parkinson's disease: Behavioral and neural studies

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**Abstract:** Parkinson's disease (PD) is characterized by a range of motor symptoms. Besides the cardinal symptoms (tremor, bradykinesia/akinesia, and rigidity), PD patients also show other motor deficits, including gait disturbance, speech deficits, and impaired handwriting. However, along with these key motor symptoms, PD patients also experience cognitive deficits in attention, executive function, working memory, and learning. Recent evidence suggests that these motor and cognitive deficits of PD are not completely dissociable, as aspects of cognitive dysfunction can impact motor performance in PD. In this article, we provide a review of behavioral and neural studies on the associations between motor symptoms and cognitive deficits in PD, specifically akinesia/bradykinesia, tremor, gait, handwriting, precision grip, and speech production. This review paves the way for providing a framework for understanding how treatment of cognitive dysfunction, for example cognitive rehabilitation programs, may in turn influence the motor symptoms of PD.

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## Introduction

Parkinson's disease (PD) is a degenerative neurological condition that affects 1–2% of the population (Kish et al., 1988). PD manifests when 60–80% of the dopaminergic neurons within the substantia nigra pars compacta (SNc) are degenerated, initially disrupting midbrain regions such as the thalamus and subthalamic nucleus, basal ganglia, globus pallidus, nucleus basalis of Meynert, and substantia nigra. This disruption is then echoed throughout various cortical areas, such as the prefrontal cortex, supplementary and primary motor cortices, as well as the cerebellum. These cortical regions are viewed as being responsible for the cardinal motor symptoms of PD, including bradykinesia, resting tremor, rigidity, gait disturbance, and postural instability (Jankovic and Tolosa, 2007; Lees et al., 2009). While these symptoms are salient characteristics of PD, there are many underlying cognitive deficits that are not so visible. These include disturbances to memory, executive function, visuospatial perception, and language (Weintraub and Burn, 2011). Each of these functions is influenced by the basal ganglia (Monchi et al., 2000; Cameron et al., 2010; Macoir et al., 2013; Caproni et al., 2014). The basal ganglia are connected with cortical regions via a complex network of parallel circuits. Five basal ganglia-thalamocortical loops have been recognized, comprising a motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate circuit. Each basal ganglia-thalamocorticol circuit receives inputs from these cortical regions and traverses specific regions of the basal ganglia and thalamus nuclei and projecting back to the cortex (Alexander et al., 1986). The operation of these circuits as fully segregated parallel loops has been challenged (Joel and Weiner, 1997), with more recent evidence supporting a degree of integration

of information across the basal ganglia-thalamocortical circuits (Haynes and Haber, 2013), allowing for interaction between the motor and cognitive circuits. The integration of these two circuits suggests that damage to one would manifest in both cognitive and motor deficits. It also suggests that treatment of cognitive deficits alongside physical therapy would be highly beneficial for the patient. Additionally, anatomical studies show that there are additional open loops (i.e. loops in which the afferent and efferent cortical areas of the basal ganglia are different) (Joel and Weiner, 1997; Graybiel, 1998). Computational models have been incorporating such open loops (Amos, 2000; Djurfeldt et al., 2001). Further, besides the frontal cortex, the occipital cortex (Seger, 2013) and medial temporal cortex (Middleton and Strick, 1996) also receive projections from the basal ganglia. It has been suggested that basal ganglia projections to these areas support visual and memory processes (Middleton and Strick, 1996; Seger, 2013). Basal ganglia projections to the prefrontal cortex has been suggested to play a role in working memory (Moustafa and Maida, 2007; Moustafa et al., 2008).

Indeed, a strong relationship between motor and cognitive processes is evident. For example, different cortical areas play a role in the cognitive processes that guide movement, including motor planning and goal-based motor processes (Matsumoto et al., 2003; Mushiake et al., 2006; Riggeal et al., 2007; Colman et al., 2009; Smulders et al., 2012; Wylie et al., 2012). Various studies in healthy individuals suggest a strong relationship between motor and cognitive processes (Matsumoto et al., 2003; Mushiake et al., 2006; Riggeal et al., 2007; Colman et al., 2009; Smulders et al., 2012; Wylie et al., 2012). However, while some studies have found clear links between motor and cognitive measures (Shine et al., 2013d; Schneider et al., 2015), these data suggest that the primary motor symptoms and cognitive deficits of PD are associated with the different clinical course of the illness. However, the interrelationships among motor and cognitive processes in PD are not well characterized. As an example, the prefrontal cortex is important for the maintenance of information (e.g. goals) in working memory, which aids production of motor responses, including hand and eye movements (Ohbayashi et al., 2003; Moustafa et al., 2013a). Indeed, locomotive dysfunction in the elderly is associated with brain volume changes (Kostic et al., 2012; Tessitore et al., 2012) and aberrant neural activity (Matsui et al., 2005) within the prefrontal cortex, suggesting a potential relationship between working memory and locomotion in PD. The dorsolateral prefrontal loop also plays a key role in motivation (Lawrence et al., 1998). So it is not surprising that some PD patients experience motivational disorders (Aarsland et al., 2009). Motivation places a value on perceived goals, so low motivation levels would affect goal-directed behaviors, which may exacerbate several PD symptoms, such as bradykinesia and gait impairments, which are discussed in the following sections. To our knowledge, the effect of motivation on these motor processes has not been studied in PD.

Currently, while the presence of the core motor symptoms remains essential for diagnosis, many PD patients demonstrate marked cognitive impairment even at the time of first presentation (Foltynie et al., 2004). Deficits across various cognitive domains including attention, working memory, and executive function have been described and tend to worsen with disease progression in tremor-dominant and akinesia-dominant (also known as akineto-rigid or non-tremor dominant) phenotypes and young-onset and rapid disease progression subgroups (Zetusky and Jankovic, 1985; Jankovic et al., 1990; Rajput, 1993; Schiess et al., 2000; Lewis et al., 2005; Zaidel et al., 2009; Mure et al., 2011; Poletti et al., 2011b; Schillaci et al., 2011; Lee et al., 2012; Moustafa and Poletti, 2013). Patients in the akinesia-dominant subgroup experience a more rapid disease progression compared to tremor-dominant patients (Louis et al., 1999; Eggers et al., 2012). Importantly, compared to tremor-dominant patients, patients with severe akinesia are more likely to experience severe cognitive impairments or even dementia (Aarsland et al., 2003; Williams-Gray et al., 2007b; Poletti et al., 2011a, 2012).

The anatomy of the neural circuitry gone awry in PD is summarized here, to serve as a reference point to be consulted throughout the following review. To begin with, the cortex, including primary motor cortex; ventral and dorsal premotor cortex; supplementary motor areas; and rostral, dorsal, and ventral cingulate areas, have one-way excitatory glutamatergic effects with the putamen, brainstem, and spinal cord, as well as a bidirectional excitatory relationship with the thalamus. The direct pathway of the putamen, which has an inhibitory GABAergic connection with the internal segment of the globus pallidus and substantia nigra pars reticulata, receives glutamatergic excitation from the SNc and thalamus. The indirect pathway of the putamen has an inhibitory GABAergic effect on the external segment of the globus pallidus, which itself goes on to inhibit the internal segment of the globus pallidus and substantia nigra pars reticulata. The subthalamic nucleus is inhibited by this indirect pathway of the putamen but in turn sends excitatory signals back to the external segment of the globus pallidus, as well as to the cortex, internal segment of the globus pallidus, substantia nigra pars reticulata, and pedunculopontine nucleus

(PPN), which itself finally excites the brainstem and spinal cord and bidirectionally inhibits the thalamus and its subcomponents (DeLong and Wichmann, 2007).

This review addresses cognitive-motor relationships in PD, describing how specific changes in cognitive function are associated with changes in motor performance. We aim to achieve this by highlighting the specific aspects of the motor symptoms in PD that are associated with cognitive deficits and suggest that they may have a common pathophysiology.

## Akinesia/bradykinesia

Akinesia and bradykinesia are considered among the primary motor features in PD. These symptoms are characterized by difficulty initiating movements, poverty of action, slowness of movements, a lack of spontaneous movement (such as swinging of the arms during walking, automatic blinking, changes of facial expression, or gesturing during speech) as well as sequential movements, which are affected due to difficulties in transitions between subcomponents of movement (Berardelli et al., 2001). Studies have found that PD patients with akinesia have more dopamine loss in the basal ganglia than do PD patients with predominant tremor symptoms (Schillaci et al., 2011), with basal ganglia dysfunction considered to be the neural mechanism underlying bradykinesia symptoms (Berardelli et al., 2001). Dopamine is excitatory on the direct ("Go") pathway, which facilitates responding, whereas it is inhibitory on the indirect ("No Go") pathway, suppressing a response (Frank and O'Reilly, 2006). A reduction in dopamine levels in PD therefore results in difficulty initiating movements and slowness of movements. Notably, computational and mechanistic models suggest that the source of akinesia involves hyperexcitability of striatal neurons originating in the indirect pathway leading to suppression of movement (Wiecki and Frank, 2010; Collins and Frank, 2014). In addition, cholinergic neurotransmission plays a critical role in controlling voluntary movement. As dopamine levels in the striatum decrease, cholinergic levels increase, suggesting that an imbalance of these neurotransmitters may underlie the motor symptoms of PD (Zhao-Shea et al., 2010).

### Associations with cognitive dysfunction

Dopamine plays not only a crucial role in motor function; it also substantially influences a diversity of cognitive processes. Therefore, it is not surprising that akinesia-dominant PD patients often show a more severe pattern of cognitive or executive dysfunction (Jankovic et al., 1990; Vakil and Herishanu-Naaman, 1998; Lewis et al., 2005; Burn et al., 2006; Lyros et al., 2008; Oh et al., 2009; Domellof et al., 2011). For example, studies have shown an association between akinesia and poor performance on tests of executive function that are dopamine dependent, such as probabilistic learning tasks (Moustafa et al., 2013b). This pattern was also present in other studies in which PD patients with predominant tremor were less impaired than akinesia-dominant PD s at performing procedural learning tasks, including the Tower of Hanoi task (Vakil and Herishanu-Naaman, 1998), as well as on working memory (Domellof et al., 2011; Poletti et al., 2012) and set shifting (Domellof et al., 2011, 2013; Poletti et al., 2012; Moustafa et al., 2013a). Akinesia-dominant patients were also more likely to experience bradyphrenia (slowness of thinking and information processing) (Rafal et al., 1984; Berardelli et al., 2001), suggesting more widespread cognitive disturbance than in the tremor-dominant type of PD.

Specifically, in non-medicated PD patients, reduced levels of dopamine impair learning from positive feedback, while facilitating learning from negative feedback (Wiecki and Frank, 2010; Collins and Frank, 2014). In patients on dopaminergic medication, the opposite occurs: dopamine replacement therapy facilitates learning from positive feedback, but patients are impaired at learning from negative feedback because the medication blocks the effect of normal dopamine dips (Wiecki and Frank, 2010; Collins and Frank, 2014). In addition, D2 receptor blockade results in progressively worse motor performance due to a learning process dissociable from the direct performance effects of DA blockade (Wiecki et al., 2009; Beeler et al., 2012).

Working memory and executive functions required for set shifting, for example those involved in the Wisconsin Card Sorting and the Trail Making Test, are often impaired in PD patients with the akinesia dominant subtype (Domellof et al., 2011, 2013; Poletti et al., 2012; Moustafa et al., 2013a). Working memory impairment in PD may be due to a lack of appropriate regulation of the gating mechanism of the basal ganglia, impairing information processing in the frontostriatal system (Frank et al., 2001). Similar to reinforcement learning, "Go" and "No Go" signals can facilitate and suppress the updating of information into prefrontal working memory representations (O'Reilly and Frank, 2006). Thus, the basal ganglia is assumed to operate as a gating mechanism to modulate information updates to

the prefrontal cortex (Frank et al., 2001; O'Reilly and Frank, 2006).

Furthermore, set-shifting deficits in non-medicated PD patients are also consistent with an inability to update a new attentional set, while medicated patients show attentional shifting deficits when having to ignore distractors that had previously been task relevant (Moustafa et al., 2008). It has been suggested that set-shifting abnormalities may result from a paroxysmal over-excitation within the output nuclei of the basal ganglia circuitry (Lewis and Barker, 2009). Thus, akinesia/bradykinesia, as well as certain cognitive deficits in PD, is likely due to dopamine depletion within the basal ganglia, possibly impairing an optimal basal ganglia output selection.

Moreover, tests of working memory and attention have robust correlations with cortical cholinergic activity. Cholinergic system degeneration and dysfunction are significant contributors to cognitive impairment in PD (Pagano et al., 2015). Cognitive deficits caused by prefrontal dopaminergic changes in PD are likely to be augmented by a cholinergic component (Bohnen and Albin, 2011). Furthermore, the akinesia phenotype is also associated with the development of dementia. Again, basal forebrain cholinergic system degeneration appears early in PD and worsens coincident with the appearance of dementia (Bohnen and Albin, 2011; Gratwicke et al., 2015a).

Non-tremor-dominant PD patients display more severe cognitive and executive dysfunction than do patients with tremor-dominant PD. This is likely due to the more severe degradation of dopamine and choline systems in these patients as cognitive and executive function has a strong reliance on these two systems (Bohnen and Albin, 2011; Moustafa et al., 2013b; Pagano et al., 2015).

# Tremor

The neural substrates underlying the development of tremor in PD are still unclear. However, tremor has been associated with cerebellar, thalamic, and subthalamic nucleus abnormalities (Kassubek et al., 2002; Probst-Cousin et al., 2003; Weinberger et al., 2009; Zaidel et al., 2009; Mure et al., 2011; Helmich et al., 2012). It has also been suggested that cerebellar activation in PD patients during movement is a compensation mechanism for corticostriatal motor circuit under-activation (Yu et al., 2007; Wu and Hallett, 2013). In addition, Rosenberg-Katz et al. (2013) found that PD patients with tremor show a lower mean loss of grey matter in the pre-supplementary and primary motor areas than in non-tremor patients. A few studies argue that tremor is dopamine independent (Benamer et al., 2000, 2003; Pirker et al., 2002; Spiegel et al., 2007).

## Associations with cognitive dysfunction

Patients with the tremor-dominant subtype of PD are less often cognitively affected in comparison to akinesia-dominant patients. Several studies have shown that tremor is not associated with impaired cognitive function (Lewis et al., 2005; Elgh et al., 2009; Hall et al., 2014). Indeed, the frontostriatal pathways, which play a key role in cognitive deficits in PD, are relatively spared in patients with predominantly tremor symptoms (Lewis et al., 2005; Williams-Gray et al., 2007a,b).

# Gait impairment

Gait impairment and postural instability are hallmarks of PD. Patients with PD have reduced stride length and walking speed while double support duration and cadence rate are increased (Morris et al., 1998). During later stages of the disease, patients may also experience freezing of gait (FOG) (Lewis and Barker, 2009), wherein their walking motion ceases, often leading to falls (Rudzinska et al., 2013). Postural instability is also known to cause falls in many patients (Koller et al., 1989). PD patients may display clinical features of postural instability that are evident during quiet, undisturbed stance, such as poor anticipatory postural responses, abnormal postural sway, and inadequately organized automatic postural reactions. Performing voluntary actions, such as leaning, may reveal reduced limits of stability. Additional deficits may be evident upon disequilibrium, including slower compensatory stepping reactions, direction-specific instability, and incorrectly directed protective arm movements (Horak et al., 2005; Mancini et al., 2008; Grimbergen et al., 2009; Rocchi et al., 2012). Gait impairment and postural instability are more common among PD patients with rapid disease progression (Jankovic et al., 1990), as well as in advanced-stage rather than early-stage PD (Kim et al., 2013).

Gait disorders and postural instability respond poorly to dopaminergic drugs, which suggest that they are caused by non-dopaminergic lesions (Karachi et al., 2010). It has been shown that gait and posture are under the control of cholinergic neurons of the PPN (Lee et al., 2000), which is part of a pathway involved in the initiation, acceleration,

deceleration, and termination of locomotion. This pathway is under the control of the deep cerebellar and basal ganglia nuclei, particularly via inputs from the medial globus pallidus, substantia nigra pars reticulata, and subthalamic nucleus (Lee et al., 2000). In addition, there is accumulating evidence that implicates the basal ganglia nuclei in the performance of "automatic" behaviors, which walking normally is, and the dysfunction of the basal ganglia in PD is proposed to interfere with automatic execution of walking, which is then performed in a goal-directed fashion (Redgrave et al., 2010).

Thus, tasks such as walking, which are automated in healthy individuals, require focused attention in PD patients. Aberrant neural activity (Matsui et al., 2005) and brain volume changes (Kostic et al., 2012; Tessitore et al., 2012) within the prefrontal cortex, an area that is also important for the maintenance of information (e.g. goals) in working memory (Ohbayashi et al., 2003; Moustafa et al., 2013a), also play a key role in locomotor dysfunction. Further, functional decoupling of goal-directed frontostriatal systems might be responsible for triggering episodes of FOG. This impaired coupling would lead to the loss of inhibitory influence over the output structures of the basal ganglia (Pahapill and Lozano, 2000; Lewis and Barker, 2009; Shine et al., 2013b), potentially leading to decreased activity within in areas of the mesencephalic locomotor region that coordinate gait (Pahapill and Lozano, 2000). This phenomenon might be triggered through dopaminergic depletion in the striatum and over-activity within the subthalamic nucleus. In addition, the inconsistent effects of dopaminergic therapy on stability in PD have led some researchers to suggest that the postural and balance deficits in PD may result from lesions to both dopaminergic and non-dopaminergic nuclei (Bloem et al., 1996; Rocchi et al., 2002; Grimbergen et al., 2009).

## Associations with cognitive dysfunction

For both the pervasive and paroxysmal gait impairments in PD, there are robust and consistent links with impairments in cognition. Since gait dysfunction, postural instability, and akinesia are characteristics of PD often associated with the non-tremor-dominant phenotype (Lewis et al., 2005), associations with the aforementioned cholinergic cognitive dysfunction and development of dementia also apply to gait dysfunction in PD. In addition, a clear example of shared mechanisms is the difficulty that PD patients experience with walking while performing a concurrent cognitive task. For example, in healthy participants, studies found that texting while walking can impact gait (Schabrun et al., 2014) and overall walking performance (Demura and Uchiyama, 2009), possibly due to affecting attentional performance (Woollacott and Shumway-Cook, 2002). This effect is more prominent in patients with moderate PD, as their walking becomes impaired during simultaneous performance of a simple goal-directed secondary motor task (e.g. "walk and talk") (Bond and Morris, 2000). With the addition of a more cognitively demanding secondary task, larger variations in the gait parameters of PD patients are observed (Hausdorff et al., 2003), perhaps uncovering an underlying impairment in the allocation of or limitation of attentional resources or in neuronal efficiency. In healthy adults, dual tasking is attention demanding too, but healthy individuals tend to give priority to postural tasks. PD patients, however, adopt a "posture second" approach, increasing the risk of falls (Bloem et al., 2001).

There is also growing evidence of a striking association between FOG and executive dysfunction (Amboni et al., 2008; Naismith et al., 2010; Shine et al., 2013e; Hall et al., 2014; Walton et al., 2014). During clinical assessment, the addition of a cognitive task, such as counting out loud in multiples of seven while walking along a standardized track, can severely exacerbate the frequency and severity of freezing (Yogev et al., 2005; Ricciardi et al., 2014). Other studies have found that walking dysfunction in PD is related to difficulty in resolving response interference produced by distractors (Plotnik et al., 2011; Vandenbossche et al., 2011). Interestingly, individuals with freezing also suffer from similar deficits in cognitive tasks that require multiple shifts between cognitive sets (Naismith et al., 2010; Shine et al., 2012; Hall et al., 2014), suggesting that the pathophysiological mechanisms underlying FOG may reflect impairments in cognitive processing under temporal pressure (Shine et al., 2013c). An explanation for the concurrence of cognitive and ambulatory deficits in PD may lie in impaired compensatory processes within the brain. The loss of automatic function would necessarily force an individual to use more cognitive architecture to accomplish what would otherwise be routine tasks (such as walking), thereby decreasing the individuals' capacity to flexibly deal with changes in their surrounding environment.

Locomotive dysfunction is due to aberrant neural activity (Matsui et al., 2005) and brain volume changes (Kostic et al., 2012; Tessitore et al., 2012) within the prefrontal cortex, an area that is also important for the maintenance of information (e.g. goals) in working memory (Ohbayashi et al., 2003; Moustafa et al., 2013a). Additionally, the nucleus basalis of Meynert is located in the

forebrain, and its cholinergic neurons are known loci of degeneration in PD (for reviews, see Gratwicke et al., 2015a,b), with more severe cholinergic loss being associated with cognitive impairment. In PD, neuropathology in the nucleus basalis of Meynert leads to impairment of both arousal and selective attention, thus mediating some components of cognitive dysfunction and dementia.

In sum, there are at least two main cognitive deficits involved in gait impairments. The first is damage to the basal ganglia, which results in impairment to "automatic process," such as movement. This results in PD patients requiring more attentional resources to initiate and maintain the walking motion and postural stability. Gait impairment is much more common in akinesia/bradykinesia-dominant PD patients, implying that they also suffer the same severe cognitive and executive dysfunction. This limitation on their attentional resources, combined with the increased load required for walking, results in the gait impairments and freezing observed in this group of PD patients.

# Handwriting

Handwriting involves the coordination of finger movements as well as integration of sensory input to guide successful motor output. Evidence suggests that handwriting can be used as an early detection tool for PD (Rosenblum et al., 2013), as PD patients typically exhibit a diminutive form of handwriting known as micrographia. In an early study on PD micrographia, McLennan et al. (1972) found that it is present in a large proportion of PD patients and is dissociable from other PD motor symptoms including tremor and rigidity. In PD, micrographia may be an example of a motor decrement where amplitude is lost with repetitive movements. In addition to micrographia, handwriting in PD is characterized by a jagged contour and sharp fluctuations in velocity and acceleration profiles (Van Gemmert et al., 1999; Teulings et al., 2002). Aspects of handwriting including stroke size, peak acceleration, stroke duration, ratio between mean and standard deviation of stroke length, or duration have been used for PD diagnostics (Teulings and Stelmach, 1991; Phillips et al., 1993). Compared to healthy controls, PD patients were found to exhibit increased movement time, reduced maximum and minimum values of magnitude of pen velocity, and more velocity inversions.

Studies found that inhibition of the supplementary cortex has been shown to improve handwriting in PD (Randhawa et al., 2013). Dopaminergic treatment in PD patients resulted in marked improvements of the kinematics of handwriting movements (Tucha et al., 2006). Indeed, through computational modeling, reducing DA levels to the basal ganglia, substantia nigra, and globus pallidus external pathways also leads to a reduction in letter size, as seen in PD (Gangadhar et al., 2008; for a review, see Helie et al., 2013).

## Associations with cognitive dysfunction

In daily life, during handwriting, mental load is often present, such as simultaneous calculations or memory recall. Similar to walking, it was found that handwriting relies on cognitive processing (Thomassen and Teulings, 1985) and is sensitive to the availability of cognitive resources. For example, it was found that PD patients took significantly longer to write while dual tasking (Van Gemmert et al., 1998). However, with the provision of external cues (e.g. lines for writing), the symptoms of micrographia in PD were lessened (Oliveira et al., 1997). It is suggested that in PD patients who experience difficulties with performing automatic movements such as handwriting, adding a secondary task may increase mental load, causing a reduction in writing size, because the writing task must then be performed in a more automated manner to free resources to fulfill the requirements of the concurrently performed secondary task (Van Gemmert et al., 1998).

In PD, small handwriting was found to correlate with disease severity, motor abnormalities, as well as cognitive impairment as measured by the Mini-Mental State Examination (Wagle Shukla et al., 2012). While writing relies on sequential motor processing, that is the coordination of different fingers (Catalan et al., 1999), to our knowledge, no study has tested the relationship between these two domains in PD. However, it is not known whether this deficit is an example of a more general deficit in dual tasking and task switching and how it is affected by dopaminergic medication.

A possible mechanism explaining this reduction in the size of handwriting in PD patients may be deficits in action-perception loops or changes in sensory feedback (e.g. visual or proprioceptive). Indeed, PD patients show a discrepancy between visual and kinesthetic feedback (Teulings et al., 2002). This may be due to a degeneration of DA neurons in the nigro-striatal pathway, which may lead to impairment in scaling the size (amplitude) of movements (Contreras-Vidal and Stelmach, 1995; Contreras-Vidal et al., 1995). Despite the linguistic component of writing, the association between cognition and

motor performance is unclear for micrographia. However, importantly, the impact of optimal response selection of the basal ganglia that influences many cognitive and motor performances is also apparent in handwriting.

A number of studies have examined the role of feedback in handwriting. Since complex movement emerges out of perception-action interactions, changes in sensory feedback (e.g. visual or proprioceptive) are likely to introduce corresponding changes in motor output, such as in handwriting. Teulings et al. (2002) controlled visual feedback for healthy controls and early-stage PD patients such that only vertical gain of handwriting was altered, while leaving horizontal gain intact. Both healthy controls and PD patients showed gradual adaptation that compensated for distorted visual feedback. Another study on the effect of delayed visual feedback on handwriting found that most PD patients learned to adjust to feedback delay analogous to healthy controls (Smith and Fucetola, 1995). Of the five patients who participated in the study, only one who suffered from micrographia exhibited difficulty in adapting to delayed feedback, suggesting the further studies employing a large sample of PD patients with micrographia are needed to investigate the nature of sensory feedback and micrographia.

In sum, similar to posture and gait, impairments in handwriting in PD patients may be partly due to poor dual task control. However, there may also be an impairment of sequential motor processing that can contribute to handwriting deficits in PD patients, but more research is needed to confirm or refute this link.

# Precision grip

Precision grip (PG) is defined as a grip formed by one finger (typically the index finger) and thumb to hold a small object (Napier, 1956). This form of grip enables us to make (Marzke, 1997; Susman, 1998) and dexterously use tools (Moyà-Solà et al., 1999; Ambrose, 2001; Young, 2003; Jones and Lederman, 2006).

Although sensorimotor control may seem to function independently of the cognitive system (Flanagan and Beltzner, 2000), various studies reveal an overlap between the motor areas for skilled movements, perceptual, and cognitive functions (Olivier et al., 2007; Grafton, 2010). For example, significant influence of a word's physical representation like apple or grape (Glover et al., 2004) and numerical magnitude like numbers 1 or 9 (Badets et al., 2007; Andres et al., 2008) affect grip motor control.

## Associations with cognitive dysfunction

In concurrent motor and perceptual task performance, individuals show longer reaction times, delayed and less accurate grip size adjustment, and impaired perpetual task performance. This indicates that motor and perceptual systems share overlapping attentional resources (Hesse and Deubel, 2011; Hesse et al., 2012). The addition of a delay to an occluded target dual-task increases the grip aperture, showing that motor, visual processing, and memory utilize similar resources (Singhal et al., 2007). While attention, visual processing, memory, and motor processing employ overlapping resources, only limited aspects of PG are affected in a PG-lift task with increased cognitive load. Using a task involving PG-lift task and a complex visual search combined with counting, it was found that a longer preload phase, a higher peak and static grip force, and a higher safety margin was employed in the combined motor-cognitive task compared to motor task alone (Guillery et al., 2013). Therefore, the PG and cognitive tasks utilize similar resources for processing information.

Impairment in PG in PD has been attributed to two possible cognitive deficits, the first being poor sensory-motor coordination. There are multiple studies supporting a sensorimotor impairment in PD patients (Shine et al., 2013a; Diaz-Hung et al., 2014). Fellows et al. (1998) have demonstrated that this impairment is evident in PD patients due to excessive grip levels and delayed lifting actions. However, Gupta et al. (2013) suggest that the impairment may lie in risk-taking behaviors as part of impulse control disorders (Voon et al., 2011; Catalan et al., 2013) that are prevalent in approximately 36% of PD patients (Callesen et al., 2014). According to Gupta et al. (2013), an excessive grip is an indication of an increased "safety margin" to ensure the object does not fall. This effect is more salient in PD patients while off, than on, medication, indicating higher risk behavior, which is in line with research on the interrelationship between impulsivity and dopamine medications (Catalan et al., 2013; Piray et al., 2014). Further research aimed at investigating sensory-motor coordination and impulsive behaviors would provide greater insight into the interaction of cognition and motor control and help identify which cognitive impairments affect PG.

# Speech problems

Most PD patients develop speech and voice disorders at some point during their illness (Ho et al., 1998), including

stuttering and difficulty initiating speech. Speech in PD is often hypophonic (i.e. hypokinetic, soft speech), monotonic (i.e. speech quality tends to be soft, hoarse, and monotonous), and/or festinating (i.e. excessively rapid, soft, poorly intelligible speech) (Jankovic, 2008). Dysarthria, which refers to slurred, slow, and difficult-to-understand speech, is also common in PD. There are few studies investigating neural substrates of speech dysfunction in PD. In one study in PD, it was found that the basal ganglia plays a role in speech production and syntactic ability (Lieberman et al., 1992) as well as phonemic and semantic fluency test performance (Ellfolk et al., 2014). One recent study found that bradykinesia affects the prosody of the patients' speech (Azevedo et al., 2013), perhaps suggesting a link between speech production and dopamine in PD.

### Associations with cognitive dysfunction

Studies have found that speech and cognitive processes are not necessarily dissociable (Altmann et al., 2001; Wiseheart et al., 2009). For example, prior studies have found a correlation between verbal and cognitive measures (Lieberman et al., 1992). A recent review has also highlighted the relationship between speech production and cognitive measures in PD (Altmann and Troche, 2011). In PD, evidence suggests that both working memory and executive function processes affect speech production (Troche and Lori, 2012). Verb production also correlates with cognitive measures, such as working memory in PD (Colman et al., 2009).

## Discussion

This review investigated the relationship between cognitive processes and motor symptoms in PD, including akinesia/bradykinesia, tremor, rigidity, handwriting, and speech problems. Not surprisingly, cognitive impairments in PD are strongly related to some motor symptoms more than others are. This might be due to some cognitive processes that rely on the integrity of the basal ganglia-thalamocortical loops along with some motor operations, while others do not. In addition, as discussed above, there is evidence of an interaction between the cognitive and motor loops in the basal ganglia, as opposed to each being fully segregated. For example, PD patients with the akinesia-dominant phenotype are more likely to suffer executive dysfunction, bradyphrenia (i.e. slowness of thinking and information processing), and dementia than those with the tremor-dominant phenotype. Tremors have been suggested to not be associated with cognitive dysfunction, with the frontostriatal pathways important for healthy cognition appearing relatively spared in those patients suffering predominantly from tremors. Gait dysfunction, which is often associated with akinesia in non-tremor-dominant patients, also appears to be linked with cognitive dysfunction. Not only are attentional deficits during locomotion evident, but there is also mounting evidence of a strong association between the episodic symptom of FOG and executive dysfunction. The relationship between cognitive and motor processes in PD is less clear for handwriting and speech. Given that both handwriting and speech have a linguistic component, the lack of a clear association with cognitive dysfunction in PD is somewhat surprising.

Focusing future studies on these weaker relationships may shed some light on the interaction of cognition and motor symptoms in PD. Such research might additionally attempt to investigate these cognitive-motor symptom relationships beginning at early, preclinical stages, at which symptoms are just evident, and follow the trajectory of these unfolding impairments and the temporal and pathophysiological relationships to other symptoms. Another direction for research might be to attempt to break down motor processes into small component parts, to elucidate what types of cognitive processes are involved at each part and how cognitive dysfunction might contribute to motor impairment. The unraveling of such cognitive-motor associations is of importance as it may lead to the possibility of active interventions such as cognitive training programs for the treatment of motor impairments, including akinesia/bradykinesia, gait dysfunction, and FOG in PD patients and also older adults.

While the focus of this paper has been on the interaction of cognition and motor function in PD, there is also evidence for motivational modulation of movement speed in PD from behavioral (Ballanger et al., 2006; Shiner et al., 2012; Kojovic et al., 2014; MacDonald and Byblow, 2015) and imaging studies (Ballanger et al., 2008). Regions of the cerebral cortex that are engaged in motivation, cognition, and sensorimotor control, as well as brainstem structures, feed into the striatum and the subthalamic nucleus, the principal input nuclei of the basal ganglia. This input is important for action selection in different motor and nonmotor domains by inhibiting irrelevant internal and external stimuli. Given the structural and functional similarity in information processing across the partially segregated motor, cognitive, and limbic circuits (Alexander et al., 1986), some degree of interaction and integration

of information across circuits may occur (Joel and Weiner, 1994; Haynes and Haber, 2013). Thus, at least for some of the motor symptoms of PD, an imbalance between neurotransmitters such as dopamine and acetylcholine may underlie deficits with inhibiting irrelevant and selecting optimal responses by the basal ganglia (Aosaki et al., 2010), causing both motor and cognitive impairments.

## References


Aarsland, D., Andersen, K., Larsen, J.P., Lolk, A., and Kragh-Sorensen, P. (2003). Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch. Neurol. *60*, 387–392.

Aarsland, D., Bronnick, K., Alves, G., Tysnes, O.B., Pedersen, K.F., Ehrt, U., and Larsen J.P. (2009). The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. J. Neurol. Neurosurg. Psychiatry *80*, 928–930.

Alexander, G.E., DeLong, M.R., and Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. *9*, 357–381.

Altmann, L.J. and Troche, M.S. (2011). High-level language production in Parkinson's disease: a review. Parkinsons Dis. *2011*, Article ID 238956, 12.

Altmann, L.J., Kempler, D., and Andersen, E.S. (2001). Speech errors in Alzheimer's disease: reevaluating morphosyntactic preservation. J. Speech Lang. Hear. Res. *44*, 1069–1082.

Amboni, M., Cozzolino, A., Longo, K., Picillo, M., and Barone, P. (2008). Freezing of gait and executive functions in patients with Parkinson's disease. Mov. Disord. *23*, 395–400.

Ambrose, S.H. (2001). Paleolithic technology and human evolution. Science *291*, 1748–1753.

Amos, A. (2000). A computational model of information processing in the frontal cortex and basal ganglia. J. Cogn. Neurosci. *12*, 505–519.

Andres, M., Ostry, D.J., Nicol, F., and Paus, T. (2008). Time course of number magnitude interference during grasping. Cortex *44*, 414–419.

Aosaki, T., Miura, M., Suzuki, T., Nishimura, K., and Masuda, M. (2010). Acetylcholine-dopamine balance hypothesis in the striatum: an update. Geriatr. Gerontol. Int. *10*, S148–S157.

Azevedo, L.L.d., Reis, C.A.d.C., Souza, I.S.d., and Cardoso, F.E.C. (2013). Prosody and levodopa in Parkinson's disease. Arq. Neuropsiquiatr. *71*, 835–840.

Badets, A., Andres, M., Di Luca, S., and Pesenti, M. (2007). Number magnitude potentiates action judgements. Exp. Brain Res. *180*, 525–534.

Ballanger, B., Thobois, S., Baraduc, P., Turner, R.S., Broussolle, E., and Desmurget, M. (2006). "Paradoxical kinesis" is not a hallmark of Parkinson's disease but a general property of the motor system. Mov. Disord. *21* 1490–1495.

Ballanger, B., Baraduc, P., Broussolle, E., Bars, D.L., Desmurget, M., and Thobois, S. (2008). Motor urgency is mediated by the contralateral cerebellum in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry *79*, 1110–1116.

Beeler, J.A., Frank, M.J., McDaid, J., Alexander, E., Turkson, S., Bernardez Sarria, M.S., McGehee, D.S., and Zhuang, X. (2012). A role for dopamine-mediated learning in the pathophysiology and treatment of Parkinson's disease. Cell Rep. *2*, 1747–1761.

Benamer, H.T., Patterson, J., Wyper, D.J., Hadley, D.M., Macphee, G.J., and Grosset, D.G. (2000). Correlation of Parkinson's disease severity and duration with 123I-FP-CIT SPECT striatal uptake. Mov. Disord. *15*, 692–698.

Benamer, H.T., Oertel, W.H., Patterson, J., Hadley, D.M., Pogarell, O., Hoffken, H., Gerstner, A., and Grosset, D.G. (2003). Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: part 1. Baseline and 3-month observations. Mov. Disord. *18*, 977–984.

Berardelli, A., Rothwell, J.C., Thompson, P.D., and Hallett, M. (2001). Pathophysiology of bradykinesia in Parkinson's disease. Brain *124*, 2131–2146.

Bloem, B.R., Beckley, D.J., van Dijk, J.G., Zwinderman, A.H., Remler, M.P., and Roos, R.A. (1996). Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. Mov. Disord. *11*, 509–521.

Bloem, B.R., Valkenburg, V.V., Slabbekoorn, M., and van Dijk, J.G. (2001). The multiple tasks test. Strategies in Parkinson's disease. Exp. Brain Res. *137*, 478–486.

Bohnen, N.I. and Albin, R.L. (2011). The cholinergic system and Parkinson disease. Behav. Brain Res. *221*, 564–573.

Bond, J.M. and Morris, M. (2000). Goal-directed secondary motor tasks: their effects on gait in subjects with Parkinson disease. Arch. Phys. Med. Rehabil. *81*, 110–116.

Burn, D.J., Rowan, E.N., Allan, L.M., Molloy, S., O'Brien, J.T., and McKeith, I.G. (2006). Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J. Neurol. Neurosurg. Psychiatry *77*, 585–589.

Callesen, M.B., Weintraub, D., Damholdt, M.F., and Moller, A. (2014). Impulsive and compulsive behaviors among Danish patients with Parkinson's disease: prevalence, depression, and personality. Parkinsonism Relat. Disord. *20*, 22–26.

Cameron, I.G., Watanabe, M., Pari, G., and Munoz, D.P. (2010). Executive impairment in Parkinson's disease: response automaticity and task switching. Neuropsychologia *48*, 1948–1957.

Caproni, S., Muti, M., Di Renzo, A., Principi, M., Caputo, N., Calabresi, P., and Tambasco, N. (2014). Subclinical visuospatial impairment in Parkinson's disease: the role of basal ganglia and limbic system. Front. Neurol. *5*, 7.

Catalan, M.J., Ishii, K., Honda, M., Samii, A., and Hallett, M. (1999). A PET study of sequential finger movements of varying length in patients with Parkinson's disease. Brain *122*, 483–495.

Catalan, M.J., de Pablo-Fernandez, E., Villanueva, C., Fernandez-Diez, S., Lapena-Montero, T., Garcia-Ramos, R., and López-Valdés, E. (2013). Levodopa infusion improves impulsivity and dopamine dysregulation syndrome in Parkinson's disease. Mov. Disord. *28*, 2007–2010.

Collins, A.G. and Frank, M.J. (2014). Opponent actor learning (OpAL): modeling interactive effects of striatal dopamine on reinforcement learning and choice incentive. Psychol. Rev. *121*, 337–366.

Colman, K.S., Koerts, J., van Beilen, M., Leenders, K.L., Post, W.J., and Bastiaanse, R. (2009). The impact of executive functions on verb production in patients with Parkinson's disease. Cortex *45*, 930–942.

Contreras-Vidal, J.L. and Stelmach, G.E. (1995). A neural model of basal ganglia-thalamocortical relations in normal and parkinsonian movement. Biol. Cybern. *73*, 467–476.

Contreras-Vidal, J.L., Teulings, H.L., and Stelmach, G.E. (1995). Micrographia in Parkinson's disease. Neuroreport *6*, 2089–2092.

DeLong, M.R. and Wichmann, T. (2007). Circuits and circuit disorders of the basal ganglia. Arch. Neurol. *64*, 20–24.

Demura, S. and Uchiyama, M. (2009). Influence of cell phone email use on characteristics of gait. Eur. J. Sport Sci. *9*, 303–309.

Diaz-Hung, M.L., Blanco, L., Pavon, N., Leon, R., Estupinan, B., Orta, E., MartíDnez, K., and Fernández, I. (2014). Sensory-motor performance after acute glutathione depletion by L-buthionine sulfoximine injection into substantia nigra pars compacta. Behav. Brain Res. *271*, 286–293.

Djurfeldt, M., Ekeberg, Ö., and Graybiel, A.M. (2001). Cortex-basal ganglia interaction and attractor states. Neurocomputing *38–40*, 573–579.

Domellof, M.E., Elgh, E., and Forsgren, L. (2011). The relation between cognition and motor dysfunction in drug-naive newly diagnosed patients with Parkinson's disease. Mov. Disord. *26*, 2183–2189.

Domellof, M.E., Forsgren, L., and Elgh, E. (2013). Persistence of associations between cognitive impairment and motor dysfunction in the early phase of Parkinson's disease. J. Neurol. *260*, 2228–2236.

Eggers, C., Pedrosa, D.J., Kahraman, D., Maier, F., Lewis, C.J., Fink, G.R., Schmidt, M., and Timmermann, L. (2012). Parkinson subtypes progress differently in clinical course and imaging pattern. PLoS One *7*, e46813, 8.

Elgh, E., Domellof, M., Linder, J., Edstrom, M., Stenlund, H., and Forsgren, L. (2009). Cognitive function in early Parkinson's disease: a population-based study. Eur. J. Neurol. *16*, 1278–1284.

Ellfolk, U., Joutsa, J., Rinne, J.O., Parkkola, R., Jokinen, P., and Karrasch, M. (2014). Striatal volume is related to phonemic verbal fluency but not to semantic or alternating verbal fluency in early Parkinson's disease. J. Neural. Transm. *121*, 33–40.

Fellows, S.J., Noth, J., and Schwarz, M. (1998). Precision grip and Parkinson's disease. Brain *121*, 1771–1784.

Flanagan, J.R. and Beltzner, M.A. (2000). Independence of perceptual and sensorimotor predictions in the size-weight illusion. Nat. Neurosci. *3*, 737–741.

Foltynie, T., Brayne, C.E., Robbins, T.W., and Barker, R.A. (2004). The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain *127*, 550–560.

Frank, M.J. and O'Reilly, R.C. (2006). A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. Behav. Neurosci. *120*, 497–517.

Frank, M.J., Loughry, B., and O'Reilly, R.C. (2001). Interactions between frontal cortex and basal ganglia in working memory: a computational model. Cogn. Affect. Behav. Neurosci. *1*, 137–160.

Gangadhar, G., Joseph, D., and Chakravarthy, V.S. (2008). Understanding Parkinsonian handwriting through a computational model of basal ganglia. Neural Comput. *20*, 2491–2525.

Glover, S., Rosenbaum, D.A., Graham, J., and Dixon, P. (2004). Grasping the meaning of words. Exp. Brain Res. *154*, 103–108.

Grafton, S.T. (2010). The cognitive neuroscience of prehension: recent developments. Exp. Brain Res. *204*, 475–491.

Gratwicke, J., Jahanshahi, M., and Foltynie, T. (2015a). Parkinson's disease dementia: a neural networks perspective. Brain *138*, 1454–1476.

Gratwicke, J., Kahan, J., Zrinzo, L., Hariz, M., Limousin, P., Foltynie, T., and Jahanshahi, M. (2015b). The nucleus basalis of Meynert: a new target for deep brain stimulation in dementia? Neurosci. Rev. *37*, 2676–2688.

Graybiel, A.M. (1998). The basal ganglia and chunking of action repertoires. Neurobiol. Learn. Mem. *70*, 119–136.

Grimbergen, Y.A., Langston, J.W., Roos, R.A., and Bloem, B.R. (2009). Postural instability in Parkinson's disease: the adrenergic hypothesis and the locus coeruleus. Exp. Rev. Neurother. *9*, 279–290.

Guillery, E., Mouraux, A., and Thonnard, J.-L. (2013). Cognitive-motor interference while grasping, lifting and holding objects. PLoS One *8*, e80125, 8.

Gupta, A., Balasubramani, P.P., and Chakravarthy, S. (2013). Computational model of precision grip in Parkinson's disease: a utility based approach [original research]. Front. Computat. Neurosci. *7*, 16.

Hall, J.M., Shine, J.M., Walton, C.C., Gilat, M., Kamsma, Y.P., Naismith, S.L., and Lewis, S.J. (2014). Early phenotypic differences between Parkinson's disease patients with and without freezing of gait. Parkinsonism Relat. Disord. *20*, 604–607.

Hausdorff, J.M., Schaafsma, J.D., Balash, Y., Bartels, A.L., Gurevich, T., and Giladi, N. (2003). Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. Exp. Brain Res. *149*, 187–194.

Haynes, W.I. and Haber, S.N. (2013). The organization of prefrontal-subthalamic inputs in primates provides an anatomical substrate for both functional specificity and integration: implications for basal ganglia models and deep brain stimulation. J. Neurosci. *33*, 10.

Helie, S., Chakravarthy, S., and Moustafa, A.A. (2013). Exploring the cognitive and motor functions of the basal ganglia: an integrative review of computational cognitive neuroscience models. Front. Comput. Neurosci. *7*, 174, 16.

Helmich, R.C., Hallett, M., Deuschl, G., Toni, I., and Bloem, B.R. (2012). Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? Brain *135*, 3206–3226.

Hesse, C. and Deubel, H. (2011). Efficient grasping requires attentional resources. Vision Res. *51*, 1223–1231.

Hesse, C., Schenk, T., and Deubel, H. (2012). Attention is needed for action control: further evidence from grasping. Vision Res. *71*, 37–43.

Ho, A.K., Iansek, R., Marigliani, C., Bradshaw, J.L., and Gates, S. (1998). Speech impairment in a large sample of patients with Parkinson's disease. Behav. Neurol. *11*, 131–137.

Horak, F.B., Dimitrova, D., and Nutt, J.G. (2005). Direction-specific postural instability in subjects with Parkinson's disease. Exp. Neurol. *193*, 504–521.

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry *79*, 368–376.

Jankovic, J. and Tolosa, E. (2007). Parkinson's Disease and Movement Disorders (Philadelphia: Lippincott Williams and Wilkins).

Jankovic, J., McDermott, M., Carter, J., Gauthier, S., Goetz, C., Golbe, L., Huber, S., Koller, W., Olanow, C., Shoulson, I., et al. (1990). Variable expression of Parkinson's disease:

a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology *40*, 1529–1534.

Joel, D. and Weiner, I. (1994). The organization of the basal ganglia-thalamocortical circuits: open interconnected rather than closed segregated. Neuroscience *63*, 363–379.

Joel, D. and Weiner, I. (1997). The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry. Brain Res. Brain Res. Rev. *23*, 62–78.

Jones, L.A. and Lederman, S.J. (2006). Human Hand Function (New York: Oxford University Press).

Karachi, C., Grabli, D., Bernard, F.A., Tande, D., Wattiez, N., Belaid, H., Bardinet, E., Prigent, A., Nothacker, H.P., Hunot, S., et al. (2010). Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J. Clin. Invest. *120*, 2745–2754.

Kassubek, J., Juengling, F.D., Hellwig, B., Spreer, J., and Lucking, C.H. (2002). Thalamic gray matter changes in unilateral Parkinsonian resting tremor: a voxel-based morphometric analysis of 3-dimensional magnetic resonance imaging. Neurosci. Lett. *323*, 29–32.

Kim, S.D., Allen, N.E., Canning, C.G., and Fung, V.S. (2013). Postural instability in patients with Parkinson's disease. Epidemiology, pathophysiology and management. CNS Drugs *27*, 97–112.

Kish, S.J., Shannak, K., and Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. N. Engl. J. Med. *318*, 876–880.

Kojovic, M., Mir, P., Trender-Gerhard, I., Schneider, S.A., Pareés, I., Edwards, M.J., Bhatia, K.P., and Jahanshahi, M. (2014). Motivational modulation of bradykinesia in Parkinson's disease off and on dopaminergic medication. J. Neurol. *261*, 1080–1089.

Koller, W.C., Glatt, S., Vetere-Overfield, B., and Hassanein, R. (1989). Falls and Parkinson's disease. Clin. Neuropharmacol. *12*, 98–105.

Kostic, V.S., Agosta, F., Pievani, M., Stefanova, E., Jecmenica-Lukic, M., Scarale, A., Spica, V., and Filippi, M. (2012). Pattern of brain tissue loss associated with freezing of gait in Parkinson disease. Neurology *78*, 409–416.

Lawrence, A.D., Sahakian, B.J., and Robbins, T.W. (1998). Cognitive functions and corticostriatal circuits: insights from Huntington's disease. Trends Cogn. Sci. *2*, 379–388.

Lee, M.S., Rinne, J.O., and Marsden, C.D. (2000). The pedunculopontine nucleus: its role in the genesis of movement disorders. Yonsei Med. J. *41*, 167–184.

Lee, J.M., Koh, S.B., Chae, S.W., Seo, W.K., Kwon do, Y., Kim, J.H., Oh, K., Baik, J.S., and Park, K.W. (2012). Postural instability and cognitive dysfunction in early Parkinson's disease. Can. J. Neurol. Sci. *39*, 473–482.

Lees, A.J., Hardy, J., and Revesz, T. (2009). Parkinson's disease. Lancet *373*, 2055–2066.

Lewis, S.J. and Barker, R.A. (2009). A pathophysiological model of freezing of gait in Parkinson's disease. Parkinsonism Relat. Disord. *15*, 333–338.

Lewis, S.J.G., Foltynie, T., Blackwell, A.D., Robbins, T.W., Owen, A.M., and Barker, R.A. (2005). Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J. Neurol. Neurosurg. Psychiatry *76*, 343–348.

Lieberman, P., Kako, E., Friedman, J., Tajchman, G., Feldman, L.S., and Jiminez, E.B. (1992). Speech production, syntax comprehension, and cognitive deficits in Parkinson's disease. Brain Lang. *43*, 169–189.

Louis, E.D., Tang, M.X., Cote, L., Alfaro, B., Mejia, H., and Marder, K. (1999). Progression of parkinsonian signs in Parkinson disease. Arch. Neurol. *56*, 334–337.

Lyros, E., Messinis, L., and Papathanasopoulos, P. (2008). Does motor subtype influence neurocognitive performance in Parkinson's disease without dementia? Eur. J. Neurol. *15*, 262–267.

MacDonald, H.J. and Byblow, W.D. (2015). Does response inhibition have pre- and postdiagnostic utility in Parkinson's disease? J. Motivated Behav. *47*, 29–45.

Macoir, J., Fossard, M., Mérette, C., Langlois, M., Chantal, S., and Auclair-Ouellet, N. (2013). The role of basal ganglia in language production: evidence from Parkinson's disease. J. Parkinsons Dis. *3*, 393–397.

Mancini, M., Rocchi, L., Horak, F.B., and Chiari, L. (2008). Effects of Parkinson's disease and levodopa on functional limits of stability. Clin. Biomech. (Bristol, Avon) *23*, 450–458.

Marzke, M.W. (1997). Precision grips, hand morphology, and tools. Am. J. Phys. Anthropol. *102*, 91–110.

Matsui, H., Udaka, F., Miyoshi, T., Hara, N., Tamaura, A., Oda, M., Oda, M., Kubori, T., Nishinaka, K., and Kameyama, M. (2005). Three-dimensional stereotactic surface projection study of freezing of gait and brain perfusion image in Parkinson's disease. Mov. Disord. *20*, 1272–1277.

Matsumoto, K., Suzuki, W., and Tanaka, K. (2003). Neuronal correlates of goal-based motor selection in the prefrontal cortex. Science *301*, 229–232.

McLennan, J.E., Nakano, K., Tyler, H.R., and Schwab, R.S. (1972). Micrographia in Parkinson's disease. J. Neurol. Sci. *15*, 141–152.

Middleton, F.A. and Strick, P.L. (1996). The temporal lobe is a target of output from the basal ganglia. Proc. Natl. Acad. Sci. U S A *93*, 8683–8687.

Monchi, O., Taylor, J.G., and Dagher, A. (2000). A neural model of working memory processes in normal subjects, Parkinson's disease and schizophrenia for fMRI design and predictions. Neural Netw. *13*, 953–973.

Morris, M., Iansek, R., Matyas, T., and Summers, J. (1998). Abnormalities in the stride length-cadence relation in parkinsonian gait. Mov. Disord. *13*, 61–69.

Moustafa, A.A. and Maida, A.S. (2007). Using TD learning to simulate working memory performance in a model of the prefrontal cortex and basal ganglia. Cogn. Syst. Res. *8*, 262–281.

Moustafa, A.A. and Poletti, M. (2013). Neural and behavioral substrates of subtypes of Parkinson's disease. Front. Syst. Neurosci. *7*, 117.

Moustafa, A.A., Sherman, S.J., and Frank, M.J. (2008). A dopaminergic basis for working memory, learning and attentional shifting in Parkinsonism. Neuropsychologia *46*, 3144–3156.

Moustafa, A.A., Bell, P., Eissa, A.M., and Hewedi, D.H. (2013a). The effects of clinical motor variables and medication dosage on working memory in Parkinson's disease. Brain Cogn. *82*, 137–145.

Moustafa, A.A., Krishna, R., Eissa, A.M., and Hewedi, D.H. (2013b). Factors underlying probabilistic and deterministic stimulus-response learning performance in medicated and unmedicated

patients with Parkinson's disease. Neuropsychology *27*, 498–510.

Moyà-Solà, S., Köhler, M., and Rook, L. (1999). Evidence of hominid-like precision grip capability in the hand of the Miocene ape Oreopithecus. Proc. Natl. Acad. Sci. *96*, 313–317.

Mure, H., Hirano, S., Tang, C.C., Isaias, I.U., Antonini, A., Ma, Y., Dhawan, V., and Eidelberg, D. (2011). Parkinson's disease tremor-related metabolic network: characterization, progression, and treatment effects. Neuroimage *54*, 1244–1253.

Mushiake, H., Saito, N., Sakamoto, K., Itoyama, Y., and Tanji, J. (2006). Activity in the lateral prefrontal cortex reflects multiple steps of future events in action plans. Neuron *50*, 631–641.

Naismith, S.L., Shine, J.M., and Lewis, S.J.G. (2010). The specific contributions of set-shifting to freezing of gait in Parkinson's disease. Mov. Disord. *25*, 1000–1004.

Napier, J.R. (1956). The prehensile movements of the human hand. J. Bone Joint Surg. Br. *38-B*, 902–913.

O'Reilly, R.C. and Frank, M.J. (2006). Making working memory work: a computational model of learning in the prefrontal cortex and basal ganglia. Neural Comput. *18*, 283–328.

Oh, J.Y., Kim, Y.S., Choi, B.H., Sohn, E.H., and Lee, A.Y. (2009). Relationship between clinical phenotypes and cognitive impairment in Parkinson's disease (PD). Arch. Gerontol. Geriatr. *49*, 351–354.

Ohbayashi, M., Ohki, K., and Miyashita, Y. (2003). Conversion of working memory to motor sequence in the monkey premotor cortex. Science *301*, 233–236.

Olivier, E., Davare, M., Andres, M., and Fadiga, L. (2007). Precision grasping in humans: from motor control to cognition. Curr. Opin. Neurobiol. *17*, 644–648.

Oliveira, R.M., Gurd, J.M., Nixon, P., Marshall, J.C., and Passingham, R.E. (1997). Micrographia in Parkinson's disease: the effect of providing external cues. J. Neurol. Neurosurg. Psychiatry *63*, 429–433.

Pagano, G., Rengo, G., Pasqualetti, G., Femminella, G.D., Monzani, F., Ferrara, N., and Tagliati, M. (2015). Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry *86*, 767–773.

Pahapill, P.A. and Lozano, A.M. (2000). The pedunculopontine nucleus and Parkinson's disease. Brain *123*, 1767–1783.

Phillips, J.G., Bradshaw, J.L., Iansek, R., and Chiu, E. (1993). Motor functions of the basal ganglia. Psychol. Res. *55*, 175–181.

Piray, P., Zeighami, Y., Bahrami, F., Eissa, A.M., Hewedi, D.H., and Moustafa, A.A. (2014). Impulse control disorders in Parkinson's disease are associated with dysfunction in stimulus valuation but not action valuation. J. Neurosci. *34*, 7814–7824.

Pirker, W., Djamshidian, S., Asenbaum, S., Gerschlager, W., Tribl, G., Hoffmann, M., Brücke, T. (2002). Progression of dopaminergic degeneration in Parkinson's disease and atypical parkinsonism: a longitudinal beta-CIT SPECT study. Mov. Disord. *17*, 45–53.

Plotnik, M., Giladi, N., Dagan, Y., and Hausdorff, J.M. (2011). Postural instability and fall risk in Parkinson's disease: impaired dual tasking, pacing, and bilateral coordination of gait during the "ON" medication state. Exp. Brain Res. *210*, 529–538.

Poletti, M., Emre, M., and Bonuccelli, U. (2011a). Mild cognitive impairment and cognitive reserve in Parkinson's disease. Parkinsonism Relat. Disord. *17*, 579–586.

Poletti, M., Frosini, D., Pagni, C., Lucetti, C., Del Dotto, P., Tognoni, G., Ceravolo, R., and Bonuccelli, U. (2011b). The association between motor subtypes and alexithymia in de novo Parkinson's disease. J. Neurol. *258*, 1042–1045.

Poletti, M., Frosini, D., Pagni, C., Baldacci, F., Nicoletti, V., Tognoni, G., Lucetti, C., Del Dotto, P., Ceravolo, R., and Bonuccelli, U. (2012). Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naive patients with Parkinson's disease. J. Neurol. Neurosurg. Psychiatry *83*, 601–606.

Probst-Cousin, S., Druschky, A., and Neundorfer, B. (2003). Disappearance of resting tremor after "stereotaxic" thalamic stroke. Neurology *61*, 1013–1014.

Rafal, R.D., Posner, M.I., Walker, J.A., and Friedrich, F.J. (1984). Cognition and the basal ganglia. Separating mental and motor components of performance in Parkinson's disease. Brain *107*, 1083–1094.

Rajput, A.H. (1993). Diagnosis of PD. Neurology *43*, 1629–1630.

Randhawa, B.K., Farley, B.G., and Boyd, L.A. (2013). Repetitive transcranial magnetic stimulation improves handwriting in Parkinson's disease. Parkinsons Dis. *2013*, 751925.

Redgrave, P., Rodriguez, M., Smith, Y., Rodriguez-Oroz, M.C., Lehericy, S., Bergman, H., Bergman, H., Agid, Y., DeLong, M.R., and Obeso, J.A. (2010). Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nat. Rev. Neurosci. *11*, 760–772.

Ricciardi, L., Bloem, B.R., Snijders, A.H., Daniele, A., Quaranta, D., Bentivoglio, A.R., and Fasano, A. (2014). Freezing of gait in Parkinson's disease: The paradoxical interplay between gait and cognition. Parkinsonism Relat. Disord. *20*, 824–829.

Riggeal, B.D., Crucian, G.P., Seignourel, P., Jacobson, C.E., Okun, M.S., Rodriguez, R., and Fernandez, H.H. (2007). Cognitive decline tracks motor progression and not disease duration in Parkinson patients. Neuropsychiatr. Dis. Treat. *3*, 955–958.

Rocchi, L., Chiari, L., and Horak, F.B. (2002). Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry *73*, 267–274.

Rocchi, L., Carlson-Kuhta, P., Chiari, L., Burchiel, K.J., Hogarth, P., and Horak, F.B. (2012). Effects of deep brain stimulation in the subthalamic nucleus or globus pallidus internus on step initiation in Parkinson disease. J. Neurosurg. *117*, 1141–1149.

Rosenberg-Katz, K., Herman, T., Jacob, Y., Giladi, N., Hendler, T., and Hausdorff, J.M. (2013). Gray matter atrophy distinguishes between Parkinson disease motor subtypes. Neurology *80*, 1476–1484.

Rosenblum, S., Samuel, M., Zlotnik, S., Erikh, I., and Schlesinger, I. (2013). Handwriting as an objective tool for Parkinson's disease diagnosis. J. Neurol. *260*, 2357–2361.

Rudzinska, M., Bukowczan, S., Stozek, J., Zajdel, K., Mirek, E., Chwala, W., Wójcik-Pędziwiatr, M., Banaszkiewicz, K., and Szczudlik, A. (2013). Causes and consequences of falls in Parkinson disease patients in a prospective study. Neurol. Neurochir. Pol. *47*, 423–430.

Schabrun, S.M., van den Hoorn, W., Moorcroft, A., Greenland, C., and Hodges, P.W. (2014). Texting and walking: strategies for postural control and implications for safety. PLoS One *9*, e84312, 8.

Schiess, M.C., Zheng, H., Soukup, V.M., Bonnen, J.G., and Nauta, H.J. (2000). Parkinson's disease subtypes: clinical classification and ventricular cerebrospinal fluid analysis. Parkinsonism Relat. Disord. *6*, 69–76.

Schillaci, O., Chiaravalloti, A., Pierantozzi, M., Di Pietro, B., Koch, G., Bruni, C., and Stefani, A. (2011). Different patterns of

nigrostriatal degeneration in tremor type versus the akinetic-rigid and mixed types of Parkinson's disease at the early stages: molecular imaging with 123I-FP-CIT SPECT. Int. J. Mol. Med. *28*, 881–886.

Schneider, J.S., Sendek, S., and Yang, C. (2015). Relationship between motor symptoms, cognition, and demographic characteristics in treated mild/moderate Parkinson's disease. PLoS One *10*, 11.

Seger, C.A. (2013). The visual corticostriatal loop through the tail of the caudate: circuitry and function. Front. Syst. Neurosci. *7*, 104.

Shine, J.M., Naismith, S.L., Palavra, N.C., Lewis, S.J., Moore, S.T., Dilda, V., and Morris, T.R. (2012). Attentional set-shifting deficits correlate with the severity of freezing of gait in Parkinson's disease. Parkinsonism Relat. Disord. *19*, 388–390.

Shine, J.M., Matar, E., Ward, P.B., Bolitho, S.J., Gilat, M., Pearson, M., Naismith, S.L., and Lewis, S.J. (2013a). Exploring the cortical and subcortical functional magnetic resonance imaging changes associated with freezing in Parkinson's disease [randomized controlled trial research support, non-U.S. Gov't]. Brain *136*, 1204–1215.

Shine, J.M., Matar, E., Ward, P.B., Bolitho, S.J., Pearson, M., Naismith, S.L., and Lewis, S.J. (2013b). Differential neural activation patterns in patients with Parkinson's disease and freezing of gait in response to concurrent cognitive and motor load [research support, non-U.S. Gov't]. PLoS One *8*, e52602, 7.

Shine, J.M., Moustafa, A.A., Matar, E., Frank, M.J., and Lewis, S.J. (2013c). The role of frontostriatal impairment in freezing of gait in Parkinson's disease. Front. Syst. Neurosci. *7*, 61.

Shine, J.M., Naismith, S.L., and Lewis, S.J.G. (2013d). The differential yet concurrent contributions of motor, cognitive and affective disturbance to freezing of gait in Parkinson's disease. Clin. Neurol. Neurosurg. *115*, 542–545.

Shine, J.M., Naismith, S.L., Palavra, N.C., Lewis, S.J., Moore, S.T., Dilda, V., and Morris, T.R. (2013e). Attentional set-shifting deficits correlate with the severity of freezing of gait in Parkinson's disease. Parkinsonism Relat. Disord. *19*, 388–390.

Shiner, T., Seymour, B., Symmonds, M., Dayan, P., Bhatia, K.P., and Dolan, R.J. (2012). The effect of motivation on movement: a study of bradykinesia in Parkinson's disease. PLoS One *7*, e47138, 7.

Singhal, A., Culham, J.C., Chinellato, E., and Goodale, M.A. (2007). Dual-task interference is greater in delayed grasping than in visually guided grasping. J. Vision *7*, 5.

Smith, M.C. and Fucetola, R. (1995). Effects of delayed visual feedback on handwriting in Parkinson's disease. Hum. Mov. Sci. *14*, 109–123.

Smulders, K., van Nimwegen, M., Munneke, M., Bloem, B.R., Kessels, R.P., and Esselink, R.A. (2012). Involvement of specific executive functions in mobility in Parkinson's disease. Parkinsonism Relat. Disord. *114*, 331–335

Spiegel, J., Hellwig, D., Samnick, S., Jost, W., Mollers, M.O., Fassbender, K., Kirsch, C.M., and Dillmann, U. (2007). Striatal FP-CIT uptake differs in the subtypes of early Parkinson's disease. J. Neural. Transm. *114*, 331–335.

Susman, R.L. (1998). Hand function and tool behavior in early hominids. J. Hum. Evol. *35*, 23–46.

Tessitore, A., Amboni, M., Cirillo, G., Corbo, D., Picillo, M., Russo, A., Vitale, C., Santangelo, G., Erro, R., Cirillo, M., et al. (2012). Regional gray matter atrophy in patients with Parkinson disease and freezing of gait. AJNR Am. J. Neuroradiol. *33*, 1804–1809.

Teulings, H.L. and Stelmach, G.E. (1991). Control of stroke size, peak acceleration, and stroke duration in Parkinsonian handwriting. Hum. Mov. Sci. *10*, 315–334.

Teulings, H.L., Contreras-Vidal, J.L., Stelmach, G.E., and Adler, C.H. (2002). Adaptation of handwriting size under distorted visual feedback in patients with Parkinson's disease and elderly and young controls. J. Neurol. Neurosurg. Psychiatry *72*, 315–324.

Thomassen, A.J.W.M. and Teulings, H.L. (1985). Time, size, and shape in handwriting: exploring spatio-temporal relationships at different levels. Time, Mind, and Behavior. J.B.J.J.A. Michon, ed. (Heidelberg: Springer-Verlag), pp. 253–263.

Troche, M.S. and Lori, J.P.A. (2012). Sentence production in Parkinson disease: effects of conceptual and task complexity. Appl. Psycholinguistics *33*, 225–251.

Tucha, O., Mecklinger, L., Thome, J., Reiter, A., Alders, G.L., Sartor, H., Naumann, M., and Lange, K.W. (2006). Kinematic analysis of dopaminergic effects on skilled handwriting movements in Parkinson's disease. J. Neural. Transm. *113*, 609–623.

Vakil, E. and Herishanu-Naaman, S. (1998). Declarative and procedural learning in Parkinson's disease patients having tremor or bradykinesia as the predominant symptom. Cortex *34*, 611–620.

Van Gemmert, A.W.A., Teulings, H.L., and Stelmach, G.E. (1998). The influence of mental and motor load on handwriting movements in Parkinsonian patients. Acta Psychol. *100*, 161–175.

Van Gemmert, A.W., Teulings, H.L., Contreras-Vidal, J.L., and Stelmach, G.E. (1999). Parkinson's disease and the control of size and speed in handwriting. Neuropsychologia *37*, 685–694.

Vandenbossche, J., Deroost, N., Soetens, E., Spildooren, J., Vercruysse, S., Nieuwboer, A., and Kerckhofs, E. (2011). Freezing of gait in Parkinson disease is associated with impaired conflict resolution. Neurorehabil. Neural Rep. *25*, 765–773.

Voon, V., Gao, J., Brezing, C., Symmonds, M., Ekanayake, V., Fernandez, H., Dolan, R.J., and Hallett, M. (2011). Dopamine agonists and risk: impulse control disorders in Parkinson's disease. Brain *134*, 1438–1446.

Wagle Shukla, A., Ounpraseuth, S., Okun, M.S., Gray, V., Schwankhaus, J., and Metzer, W.S. (2012). Micrographia and related deficits in Parkinson's disease: a cross-sectional study. BMJ Open *2*, 6.

Walton, C.C., Shine, J.M., Mowszowski, L., Gilat, M., Hall, J.M., O'Callaghan, C., Naismith, S.L., and Lewis, S.J. (2014). Impaired cognitive control in Parkinson's disease patients with freezing of gait in response to cognitive load. J. Neural Transm. *122*, 653–660.

Weinberger, M., Hutchison, W.D., Lozano, A.M., Hodaie, M., and Dostrovsky, J.O. (2009). Increased gamma oscillatory activity in the subthalamic nucleus during tremor in Parkinson's disease patients. J. Neurophysiol. *101*, 789–802.

Weintraub, D. and Burn, D.J. (2011). Parkinson's disease: the quintessential neuropsychiatric disorder. Mov. Disord. *26*, 1022–1031.

Wiecki, T.V. and Frank, M.J. (2010). Neurocomputational models of motor and cognitive deficits in Parkinson's disease. Prog. Brain Res. *183*, 275–297.

Wiecki, T.V., Riedinger, K., von Ameln-Mayerhofer, A., Schmidt, W.J., and Frank, M.J. (2009). A neurocomputational account of

catalepsy sensitization induced by D2 receptor blockade in rats: context dependency, extinction, and renewal. Psychopharmacology (Berl) *204*, 265–277.

Williams-Gray, C.H., Foltynie, T., Brayne, C.E., Robbins, T.W., and Barker, R.A. (2007a). Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain *130*, 1787–1798.

Williams-Gray, C.H., Hampshire, A., Robbins, T.W., Owen, A.M., and Barker, R.A. (2007b). Catechol *O*-methyltransferase Val158Met genotype influences frontoparietal activity during planning in patients with Parkinson's disease. J. Neurosci. *27*, 4832–4838.

Wiseheart, R., Altmann, L.J., Park, H., and Lombardino, L.J. (2009). Sentence comprehension in young adults with developmental dyslexia. Ann. Dyslexia *59*, 151–167.

Woollacott, M. and Shumway-Cook, A. (2002). Attention and the control of posture and gait: a review of an emerging area of research. Gait Posture *16*, 1–14.

Wu, T. and Hallett, M. (2013). The cerebellum in Parkinson's disease. Brain *136*, 696–709.

Wylie, S.A., van den Wildenberg, W., Ridderinkhof, K.R., Claassen, D.O., Wooten, G.F., and Manning, C.A. (2012). Differential susceptibility to motor impulsivity among functional subtypes of Parkinson's disease. J. Neurol. Neurosurg. Psychiatry *83*, 1149–1154.

Yogev, G., Giladi, N., Peretz, C., Springer, S., Simon, E.S., and Hausdorff, J.M. (2005). Dual tasking, gait rhythmicity, and Parkinso's disease: which aspects of gait are attention demanding? Eur. J. Neurosci. *22*, 1248–1256.

Young, R.W. (2003). Evolution of the human hand: the role of throwing and clubbing. J. Anat. *202*, 165–174.

Yu, H., Sternad, D., Corcos, D.M., and Vaillancourt, D.E. (2007). Role of hyperactive cerebellum and motor cortex in Parkinson's disease. Neuroimage *35*, 222–233.

Zaidel, A., Arkadir, D., Israel, Z., and Bergman, H. (2009). Akinetic-rigid vs. tremor syndromes in Parkinsonism. Curr. Opin. Neurol. *22*, 387–393.

Zetusky, W.J. and Jankovic, J. (1985). Laterality and symptom association in Parkinson's disease. Arch. Neurol. *42*, 1132–1133.

Zhao-Shea, R., Cohen, B.N., Just, H., McClure-Begley, T., Whiteaker, P., Grady, S.R., Salminen, O., Gardner, P.D., Lester, H.A., and Tapper, A.R. (2010). Dopamine D2-receptor activation elicits akinesia, rigidity, catalepsy, and tremor in mice expressing hypersensitive {alpha}4 nicotinic receptors via a cholinergic-dependent mechanism. FASEB J. *24*, 49–57.